Pharmacokinetics of a Novel EVG / COBI / FTC / GS-7340 Single Tablet Regimen

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Abstract #O_13
GS-7340: Novel Prodrug of Tenofovir (TFV) Designed to Deliver TFV to Cells

- **Gut Lumen**: TDF (Viread®) → GS-7340
- **Blood**: TDF → GS-7340 → GS-7340 → TDF → TFV → TDF → TFV → TFV-DP
- **Lymphocytes**: TDF → GS-7340 → GS-7340 → TDF → TFV → TFV-DP

Diagram: Flow of Tenofovir (TFV) and TFV-DP through three compartments: Gut Lumen, Blood, and Lymphocytes.
GS-7340 Profile

• In Vitro Features vs TDF
  – Greater potency and ~200-fold more stable in plasma: circulating prodrug
  – Rapidly metabolized by Cathepsin A in lymphoid cells

• Antiviral Activity vs TDF as monotherapy
  – GS-7340 ≥ 25 mg QD provides greater HIV-1 RNA drop (1.5 to 1.7 log₁₀ c/ml) vs TDF (~0.9)

• Pharmacokinetics vs TDF
  – Circulating plasma exposures of GS-7340 (~ 5 hrs post-dose)
  – 7-fold higher TFV-DP in PBMC at 1/10th TDF dose
  – ~90% lower circulating TFV in plasma

• Potential for new single-tablet regimens (STRs) with a range of HIV drug classes
  – EVG/COBI/FTC/TDF (QUAD) highly efficacious and well tolerated in Phase 3 studies of treatment-naïve patients

Lee W et al. AAC 2005; Markowitz M et al. CROI 2011; Ruane P et al. CROI 2012; Sax et al. CROI 2012; DeJesus et al. CROI 2012
Elvitegravir/Cobicistat/Emtricitabine/GS-7340

- EVG/COBI/FTC/GS-7340 assessment from three Phase 1 studies
  - Multiple dose PK of EVG/COBI/FTC/GS-7340 STR
  - Drug interaction potential between GS-7340 and COBI
  - Selection of GS-7340 dose for STR clinical development

- Study Designs
  - Study 1
    - 4 x 4 crossover of EVG/COBI/FTC/GS-7340 25 mg or 40 mg, EVG/COBI/FTC/TDF (QUAD) and GS-7340 single agent 25 mg
  - Study 2
    - Fixed sequence crossover: GS-7340 8 mg alone, with COBI 150 mg
  - Study 3
    - Two, 2-way crossover cohorts
      - Cohort 1: EVG/COBI/FTC/GS-7340 10 mg, EVG/COBI
      - Cohort 2: EVG/COBI/FTC/GS-7340 10 mg, FTC/GS-7340 25 mg
Demographics and Safety

- All treatments were generally well tolerated
- No Grade 3/4 adverse events observed across studies
- One discontinuation in Study 1 due to AE (Grade 2 rhabdomyolysis) while receiving GS-7340 25 mg

<table>
<thead>
<tr>
<th></th>
<th>Study 1 (n=20)</th>
<th>Study 2 (n=12)</th>
<th>Study 3 (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>10 males 10 females</td>
<td>8 males 4 females</td>
<td>24 male 10 female</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>37 (25-45)</td>
<td>33 (22-44)</td>
<td>32 (18-45)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.2 (63.2-102)</td>
<td>78.5 (64.0-105)</td>
<td>74.9 (46.6-104)</td>
</tr>
<tr>
<td>Race</td>
<td>17 White 3 Black</td>
<td>9 White 3 Black</td>
<td>20 White 14 Black</td>
</tr>
</tbody>
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Presented at the 13th Int. Workshop on Clin. Pharmacology of HIV Pharmacology – 2012, Barcelona Spain
Study 1 Results: GS-7340 and Tenofovir PK
STR with GS-7340 25 mg or 40 mg

<table>
<thead>
<tr>
<th></th>
<th>GS-7340</th>
<th></th>
<th>Tenofovir</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>STR 25 mg</td>
<td>STR 40 mg</td>
<td>GS-7340 25 mg</td>
<td>STR 25 mg</td>
</tr>
<tr>
<td>AUC (ng.hr/ml)</td>
<td>552 (41)</td>
<td>930 (34)</td>
<td>242 (42)</td>
<td>835 (18)</td>
</tr>
<tr>
<td>C_max (ng/ml)</td>
<td>507 (54)</td>
<td>793 (52)</td>
<td>215 (55)</td>
<td>66 (51)</td>
</tr>
<tr>
<td>C_tau (ng/ml)</td>
<td>-</td>
<td></td>
<td>28 (20)</td>
<td>45 (21)</td>
</tr>
</tbody>
</table>

- GS-7340 and TFV plasma exposures higher as STR vs GS-7340 alone.

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Study 1 Results: EVG, COBI, and FTC PK
STR with GS-7340 25 mg or 40 mg

- EVG, COBI, and FTC PK similar between GS-7340 STR and QUAD

![Graphs showing EVG, COBI, and FTC concentrations over time for different treatments.](attachment:graphs.png)
Study 2 Results: GS-7340 and Tenofovir PK

GS-7340 8 mg with COBI 150 mg

<table>
<thead>
<tr>
<th></th>
<th>GS-7340 8 mg + COBI</th>
<th>GS-7340 8 mg</th>
<th>GS-7340 8 mg + COBI</th>
<th>GS-7340 8 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (% CV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC (ng.hr/ml)</td>
<td>188 (27)</td>
<td>81 (44)</td>
<td>287 (22)</td>
<td>86 (19)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>142 (33)</td>
<td>71 (73)</td>
<td>19 (21)</td>
<td>5.8 (20)</td>
</tr>
<tr>
<td>C&lt;sub&gt;tau&lt;/sub&gt; (ng/ml)</td>
<td></td>
<td>10 (24)</td>
<td>3.0 (20)</td>
<td></td>
</tr>
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</table>

• GS-7340 STR findings driven by COBI (inhibition of intestinal Pgp-efflux)
Study 3 Results: GS-7340 PK
STR with GS-7340 10 mg

<table>
<thead>
<tr>
<th>GS-7340 PK Parameter</th>
<th>STR 10 mg</th>
<th>FTC/GS-7340 25 mg</th>
<th>GMR (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC$_{\text{last}}$ (ng.hr/ml)</td>
<td>250 (25)</td>
<td>278 (29)</td>
<td>91.4 (84.1, 99.4)</td>
</tr>
<tr>
<td>C$_{\text{max}}$ (ng/ml)</td>
<td>177 (35)</td>
<td>180 (34)</td>
<td>98.7 (84.6, 115)</td>
</tr>
</tbody>
</table>

- STR with GS-7340 10 mg provides similar exposures as GS-7340 25 mg.
Study 3 Results: Tenofovir PK
STR with GS-7340 10 mg

<table>
<thead>
<tr>
<th>TFV PK; Mean (%CV)</th>
<th>STR 10 mg</th>
<th>FTC/GS-7340 25 mg</th>
<th>GMR (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$AUC_{\tau}$ (ng.hr/ml)</td>
<td>324 (15)</td>
<td>266 (22)</td>
<td>124 (117,131)</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>20 (14)</td>
<td>19 (76)</td>
<td>114 (97.5,134)</td>
</tr>
<tr>
<td>$C_{\tau}$ (ng/ml)</td>
<td>11 (18)</td>
<td>9.2 (24)</td>
<td>125 (118,134)</td>
</tr>
</tbody>
</table>

STR with GS-7340 10 mg: Comparable TFV vs GS-7340 25 mg; 90% lower TFV exposure vs QUAD
Study 3 Results: EVG, COBI, and FTC PK STR with GS-7340 10 mg

- EVG, COBI, and FTC PK similar between GS-7340 STR and EVG/COBI or FTC single agent
Conclusions

• GS-7340 and TFV exposures ~2-3-fold higher with COBI or as EVG/COBI/FTC/GS-7340 STR
  – Driven by COBI inhibition of intestinal Pgp-mediated intestinal secretion of GS-7340

• EVG/COBI/FTC/GS-7340 10 mg provided comparable GS-7340 and TFV PK as GS-7340 25 mg, ~90% lower TFV exposure vs QUAD

• EVG/COBI/FTC/GS-7340 STR provided similar EVG, COBI, and FTC PK vs single agents (EVG/COBI and FTC)

• A Phase 2 study comparing EVG/COBI/FTC/GS-7340 STR vs QUAD ongoing